32 Bipolar Disorder

An Environmental and Nutritional Approach to Therapy

Alan R. Vinitsky, M.D., and Ronald R. Parks, M.D.

INTRODUCTION

Bipolar illness (BPI) is a major cause of pain and suffering for which conventional medical and psychiatric treatments provide but modest remediation. BPI is characterized by bouts of illness with relatively disease-free states in between and subclinical states as well. Therefore, BPI can be viewed as a continuum of disease, where it may be possible to consider underlying metabolic aberrations associated with the disease state. A continuum model of BPI further allows interconnected disciplines of psychophysiology, biochemistry, psychopharmacology, toxicology, genetics, psychology, sociology, as well as nutritional, environmental, and psychiatric medicine to inform treatment decisions. In this chapter, environmental and nutritional models offer insights into disease prognosis and prevention of relapse.

DEFINITION AND EPIDEMIOLOGY

The official nomenclature has been codified and defined in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV-TR*, with *DSM-V* anticipated) [1]. Bipolar I disorder describes a sufferer who experienced distinct periods of severe depression alternating with at least one episode of severe activation or mania, while bipolar II disorder had no distinct mania (see Table 32.1).

Both bipolar I and bipolar II can be devastating and severe. The difference between them is that by definition bipolar I must have had at least one manic episode, while bipolar II can present with hypomania. Mania may later present in a bipolar II individual, resulting in reclassification. Recurrent depression is characteristic of both conditions, and the depth of the depression usually determines overall severity. Some subtler bipolar I—more often bipolar II—present with irritability, anxiety, and moodiness, and alternating hard-to-define recurrent depression. Bipolar spectrum illness has been defined as recurrent depression with milder periods of activation (hypomania) and less dramatic symptoms [2].

Clinical presentations tend to vary. Diagnosed depression is often bipolar disorder misdiagnosed [3,4]. Additional clues to diagnosis include: poor response to treatments for depression, mania, psychosis, or induced rapid mood fluctuations triggered by antidepressants, family history of bipolar illness, onset of recurrent depression before the 20s, severe premenstrual syndrome (PMS) or premenstrual dysphoria syndrome (PMDS), postpartum depression, atypical depressions with a lot of irritability, sleep disturbance, and anxiety. Presentations of BPI in the older population (> 50 years) more often have comorbidities at the time of diagnosis, including cognitive changes [5].

TABLE 32.1
Bipolar Disorder I and II Characteristics

Bipolar Classification	Type I	Type II	Cyclothymia
Presentation	Distinct period of abnormal mood with at least one manic episode	Distinct period of mood change with no mania to date	Distinct periods of mood change less severe than type 1 or 2
Mood	1. Persistently elevated, expansive 2. Irritable mood 3. May include psychotic symptoms	At least one hypomanic episode	Fluctuation
Additional Symptoms 1. Unusually confident 2. Inflated self-esteem 3. Needs less sleep 4. Unusually talkative or pressure to keep talking 5. Racing thoughts or flight of ideas 6. Trouble concentrating 7. Distractibility 8. More goal-directed activity 9. Engages in pleasurable, high-risk activities, with painful consequences 10. Acts strangely	Three symptoms or four if irritable mood is present	Three symptoms or four if irritable mood is present	Symptoms are milder
Duration	At least seven days	At least four days	Fewer days
Depression	Usually one or more	One or more	Multiple cycles

Note: Based on *DSM IV-TR* criteria—the term bipolar spectrum disorder includes cyclothymia. Rapid cycling of any of the aforementioned applies to four or more mood changes in one year.

BPI is not uncommon. The epidemiology and lifetime prevalence estimates are 1.0% for bipolar I disorder, 1.1% for bipolar II disorder, and 2.4% to 4.7% for sub-threshold BPI [2,6]. Age at onset ranges from childhood to mid-20s and later, and BPI is unusual after the fourth decade. Recurrence rates of BPI over a five-year period are close to 100%, with periods of no symptoms, minor symptoms, or with more significant residual symptoms.

At its worst, it can lead to higher mortality from suicide and concurrent medical illness. Among psychiatric disorders, BPI has one of the highest rates of mortality from suicide—bipolar II is greater than bipolar I. Unrecognized co-occurrence of BPI and medical illness can lead to ineffectual treatment and poor outcomes. Six months after suffering myocardial infarction, victims with major depression (commonly seen in BPI) had six times the mortality of nondepressed patients [7].

Recurrence of bipolar episodes with depression, mania, or hypomania has adverse effects on family, social, and occupational functioning [8–13]. BPI disrupts normative functioning across spheres: social functioning such as failures of social relationships and work life, productivity, sleep disturbance, anxiety, depression, overactivation of mind or behavior (i.e., mania or hypomania), and irritability; cognitive functioning with impaired thinking and distraction; physical well-being with somatic pain and propensity for addictions; and emotional functioning evidenced by impulsivity, loss of interest or pleasure and of motivation, and suicidal thinking [14,15].

Appreciating the breadth of impairment adds urgency to diagnosis and initiation of treating any underlying metabolic dysfunction. Effectively treated, bipolar I sufferers—even those with recurrent hospitalizations for mania and depression—can become stable, functional, and productive for years.

PATHOGENESIS

Genetics and the Early Environment

Epidemiologic studies support genetic risk factors in BPI. First-degree relatives of people with BPI are seven times more likely to develop bipolar I than the general population. Adopted children whose biologic parents have either BPI or a major depressive disorder remain at increased risk of developing an affective disorder. However, identical twins develop BPI at wide-ranging concordance rates of 33–90%, pointing to environmental factors affecting expression of susceptibility genes [16]. ANK3, CACNA1C, and CLOCK genes are identified in BPI, especially bipolar I [17–23].

Advanced parental age (APA) is an established risk factor for BPI [24]. APA is a summary marker because it reflects both elevated risk for genetic mutations and epigenetic factors.

Epigenetic factors also influence gene expression. The epigenome is a layer above the genetic code that regulates DNA depending on environmental inputs. Methylation of DNA, histones, and microsomal RNA is critical in suppressing or expressing certain genes that present as BPI or other neuropsychiatric disorders [25–29]. Examples include hypomethylation of serotonin type 2-A gene (HTR2A at T102C polymorphic site) [30], MB-COMT promoter [31], GAD1 promoter [32], and noncoding microRNA, which affects DISC1 and DISC2 [33] each of which increase the expression of BPI. In a postmortem brain tissue study, the hippocampus is a site of decreased mRNA expression of 43 mitochondrial oxidative phosphorylation and ATP-dependent processes [34]. Other loci of genetic change include the frontal and temporal lobes.

Epigenetic factors are of particular interest because methylation of DNA not only affects genetic expression in utero, it affects genetic expression throughout life, albeit to a much lesser extent, affording an opportunity to modify outcomes through facilitating impaired methylation.

External Environmental Factors

BPI symptomatology is influenced by physical, chemical, and biologic factors in the external environment (Table 32.2). An example of a biologic factor is Pediatric Autoimmune Neuropsychiatric

TABLE 32.2
Environmental Factors

Biological	Chemical	Physical
Algae	Air pollutants	Desynchronosis resulting from travel across time zones or shift work
Bacteria	Heavy metals	Geographic latitude and elevation
Molds and Yeasts	Pesticides	Natural disasters
Parasites	Solvents and other volatile organic compounds	Particulates and other physical matter from construction
Viruses	Water pollutants	Radiation
Worms		Trauma

Many of these factors influence a person's health on a continuing basis. They must be considered in the context of explaining why (s)he is expressing symptoms, such as anxiety or depression. These factors are ordinarily ignored because they are so commonplace. For 15–30% of the population [79], environmental exposures are a source of stress on the autonomic nervous system and metabolic pathways. Inflammation may develop over time, resulting in symptoms such as anxiety or depression. In a chronic state, those symptoms may be indistinguishable from bipolar disorder. Multiple opportunities exist for extensive environmental exposure. Water damage in home, work, and school may promote a setting for microbes and generate particulates. Unexpected natural disasters and terrorist attacks could release radiation. Combustion of debris and fuel oil provide additional contaminations.

Disease Associated with Streptococcal infection (PANDAS). Since other infections and noninfectious environmental exposures can trigger a similar response, the term has been broadened to Pediatric Acute Onset Neuropsychiatric Syndrome (PANS). Metabolic effects of biotoxins including mycotoxins, and possible treatment approaches are detailed in this book (Chapter 44: Biotoxins and Chapter 43: Mycotoxin-Related Illness).

An example of a chemical factor is mercury exposure, giving rise to the expression "mad as a hatter." Haberdashers had an occupational exposure to mercury-cured furs.

An example of a physical factor is springtime in high-latitude environments, where changes in solar, barometric, and other factors in the physical environment exert effects significant enough to trigger BPI. Concurrent depletion of nutrients from diminished intake of fruits/vegetables in spring may also predispose, as can seasonal allergies [35]. Another physical factor may be exposure to ionizing and/or nonionizing radiation (Chapter 42: Electromagnetic Hypersensitivity).

Figure 32.1 [36] illustrates how diverse factors from our external environment alter the internal chemical environment, thereby predisposing us or protecting us from disease states to which we are vulnerable. Summary lab tests, more of which will be forthcoming from ongoing "omics" research, serve as biomarkers for the treatment-responsive underlying pathophysiology.

Internal Factors, Specifically Methylation

Methylation and aberrations in the methylation pathways are aspects of the internal chemical environment central to BPI pathophysiology. The rationale is as follows:

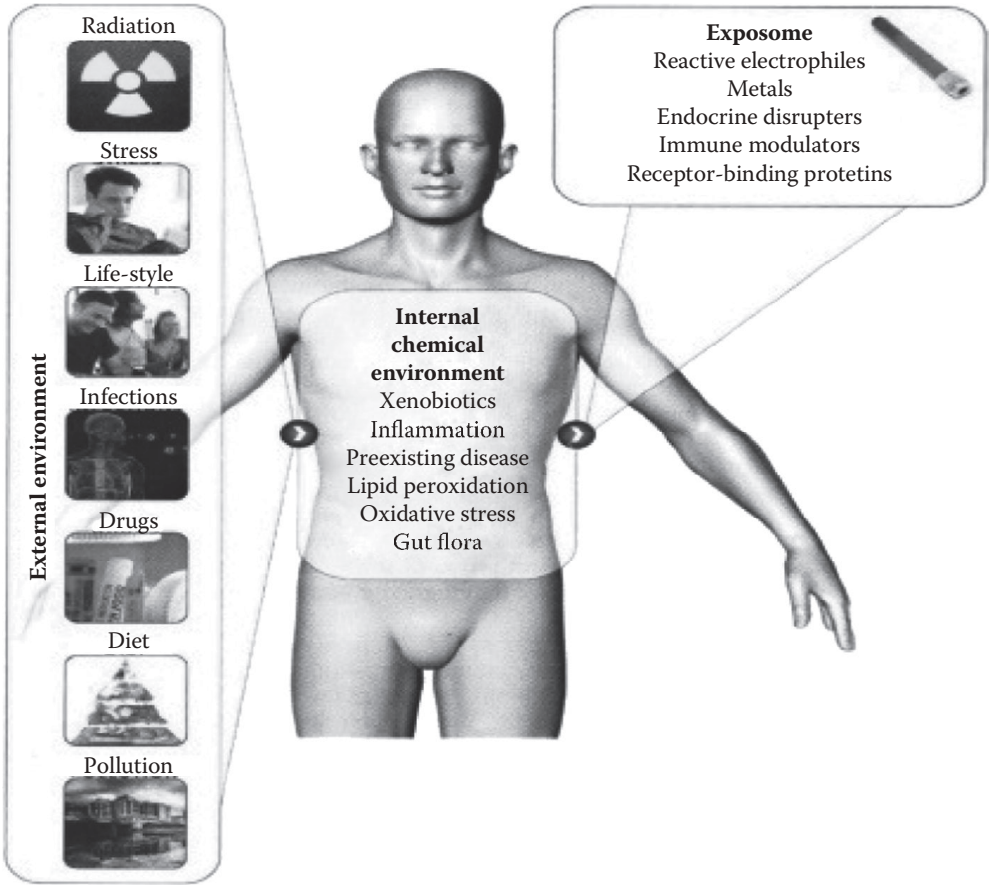

FIGURE 32.1 The exposome is influenced by external environmental factors and the internal chemical environment. Reproduced with permission from Rappoport 2010.

- An unknown but substantial portion of BPI expression results from the epigenomic effects of hypomethylation.
- Methylation generates adrenalin from norepinephrine and inactivates adrenalin, norepinephrine, and dopamine. Insufficient methylation can result in excess neurotransmitters that exacerbate anxiety.
- The first metabolite of acetylcholine includes the intrinsic production of formaldehyde, which raises sympathetic nervous system (SNS) activity, resulting in anxiety.
- Concurrent with inadequate methylation, protein destruction is ongoing, and synthesis of proteins and neurotransmitters is insufficient.
- Methylation is associated with reduction of bipolar gene expression, improvement in production and metabolism of neurotransmitters, stabilizing the autonomic nervous system (ANS), and improvement of comorbid conditions.

The production of S-adenosylmethionine (SAMe) is required for more than 50 methylation pathways present throughout the body [37]. SAMe is generated (Figure 32.2) by recycling methionine, an essential amino acid, through homocysteine, which is toxic at high levels.

Human biology has evolved a redundant pathway that bypasses the folate and hydroxocobalamin remethylation process of Figure 32.2. The redundant pathway is utilized when inadequate folate and hydroxocobalamin are available for the primary pathway and when methylation demands are excessive. The redundant pathway depends on betaine and zinc.

Methylation is a phase II detoxification pathway and as such influences neurohormonal and neurotransmitter balances. Methyl transferases use SAMe to methylate. Catechol-O-methyltransferase (COMT) processes adrenalin, norepinephrine, dopamine, l-dopa, methyldopa, and catechol estrogens. Vulnerability is in part genetic, since a single nucleotide polymorphism of COMT can lead to impaired metabolism of catechols and result in increased anxiety, which further potentiates the risk for BPI. Methylation inactivates histamine, serotonin, and converts melatonin from serotonin [38]. SAMe donates a methyl group to process estrogen, xenoestrogens, many heavy metals, and niacin, synthesize RNA, repair DNA, and create creatine.

Oxidative Stress and Methylation

The primary methylation resources to ensure ample supply of SAMe are: folic acid, hydroxocobalamin, and reduced-glutathione. Their interaction is illustrated in Figures 32.3 and 32.4.

Oxidative stress increases malondialdehyde [39] and other aldehydes. Inflammation stress raises nitric oxide [40] and lowers glutathione. The degradation of glutathione (GSH) by increased gamma-glutamyl transaminase (GGT) further lowers GSH, while generating glutamate. Life stress also generates the same stress markers, and the concomitant need for increased ascorbate further depletes active reduced GSH.

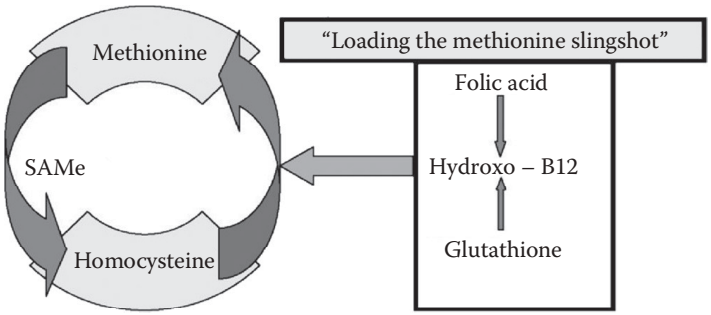

FIGURE 32.2 Loading the methionine slingshot: Methionine must ultimately be available to generate SAMe. In the simplest form of the "slingshot," hydroxcocobalamin is activated by reduced glutathione. Activated folic acid then donates a methyl group to hydroxocobalamin yielding methylcobalamin.

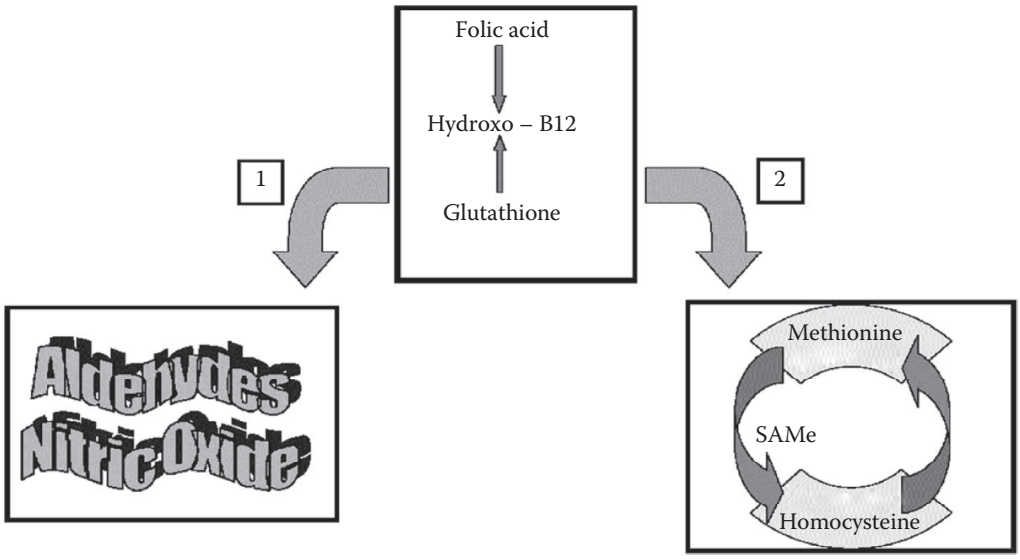

FIGURE 32.3 Stress marker cleanup is a necessary prerequisite to production of SAMe. 1) Folic acid (folate) scavenges for malondialdehyde and other aldehydes. Hydroxcobalamin (OH-B12) scavenges for nitric oxide, and reduced glutathione is depleted as it scavenges for toxins, such as mercury, pesticides, and solvents, or is oxidized while functioning as an antioxidant. 2) If one or more of these three scavengers is in short supply, methylation will be compromised for a lack of sufficient SAMe. Pharmacologic dosing of folate and hydroxycobalamine (OH-B12) in sufficient doses are required to clean up aldehydes and nitric oxide.

The enzyme paraoxonase is another place in the methylation pathways vulnerable to nutrient depletion and environmental toxicants, as shown in Figure 32.5.

Inflammation and Methylation

BPI has confirmed increased inflammation, separate from hypomethylation, yet with several intersecting pathways, such as nitric oxide synthase (iNOS) [41]. Cleanup of inflammation begins with hydroxocobalamin (see Figure 32.4) scavenging for nitric oxide. As cortisol levels decrease when stress is reduced, inflammation may become more noticeable. As immune mechanisms strengthen, increased cellular, antibody, and cytokine inflammatory responses are observed. This transformation permits detection of previously hidden etiologies for psychiatric and other symptoms as antibody production may become more robust.

Another aspect of inflammation is the excitatory effect of glutamate on the *N*-Methyl-D-Aspartate (NMDA) receptor. An additional observation is that there is glutamate spillover in its regulation of synapses [42]. Glutamate rises in response to elevated cortisol and stimulates the NMDA receptor. Folate is part glutamate. An enzyme, folylpolyglutamate synthase, can attach multiple glutamate molecules one at a time to folate [43]. Therefore, folate likely functions as a glutamate scavenger and storage molecule because it does not participate in methylation in the polyglutamate form.

A notable inflammatory brain toxic response is the production of quinolinic acid, which is a metabolite of the alternate tryptophan pathway in the production of niacinamide (Figure 32.6). These metabolic pathways converge at the NMDA receptor as shown in Figure 32.7.

Several nutrients available as dietary supplements exert their therapeutic effects on the Figure 32.6 pathway. Epigallocatechin gallate in green tea [44] and curcumin [45] from the spice turmeric block the NMDA receptor from stimulation by quinolinic acid. D-ribose, the five-carbon sugar precursor to ATP, may further promote the conversion of quinolinic acid to niacinamide. Sufficiently high doses of niacinamide 500 mg administered twice daily can push back on quinolinic acid production, thereby reducing its neurotoxic effect. Other powerful anti-inflammatories include quercetin, which

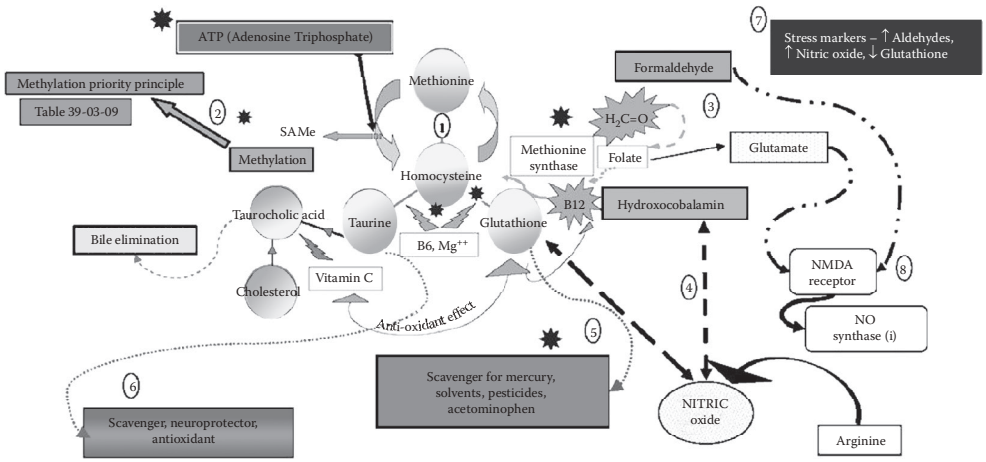

FIGURE 32.4 Sustaining methylation:

1. Methionine + Adenosine → S-Adenosyl Methionine (SAMe) → S-Adenosyl Homocysteine → Homocysteine → Methionine.
2. Methylation need is increased when an individual is stressed. Specific stressors requiring methylation further exacerbate the stressed state, thereby destabilizing the autonomic nervous system.
3. Folate scavenges for aldehydes and glutamate and recycles aldehydes through hydroxocobalamin (OH-B12) to homocysteine.
4. OH-B12 is reduced by glutathione but also scavenges for nitric oxide (NO) and peroxynitrite. OH-B12 can be inactivated by NO.
5. Glutathione (GSH) scavenges for mercury, pesticides, solvents, and acetominophen. GSH can be inactivated by NO, reduces vitamin C (ascorbate) or is reduced by it.
6. Taurine scavenges for hypochlorite and other chlorine-containing compounds. Taurine, magnesium, and vitamin B6 (pyridoxine) encourage the production of GSH, when homocysteine is converted to cysteine.
7. Oxidative physical and emotional stresses lead to increased aldehydes, nitric oxide, and oxidized glutathione (or less available reduced GSH).
8. Nitric oxide causes increased pain and inflammation through the inducible nitric oxide synthase (iNOS) pathway, which is potentiated by formaldehyde, glutamate, quinolinic acid (derived from tryptophan), carbon monoxide (from heme degradation via hemoxygenase), acidity, and solvents.

* indicates six pathways where mercury interrupts support of methylation: When nutrients are diverted for scavenging or are inactivated alone or in combination, methylation will become inadequate under stress. If OH-B12 is insufficient or dysfunctional, then methylation cannot adequately proceed. When GSH is insufficient or dysfunctional, OH-B12 is dysfunctional. In either instance, folate becomes functionally insufficient, even when levels are elevated, because it is saturated with methyl groups and aldehydes. This condition is called the folate trap [80].

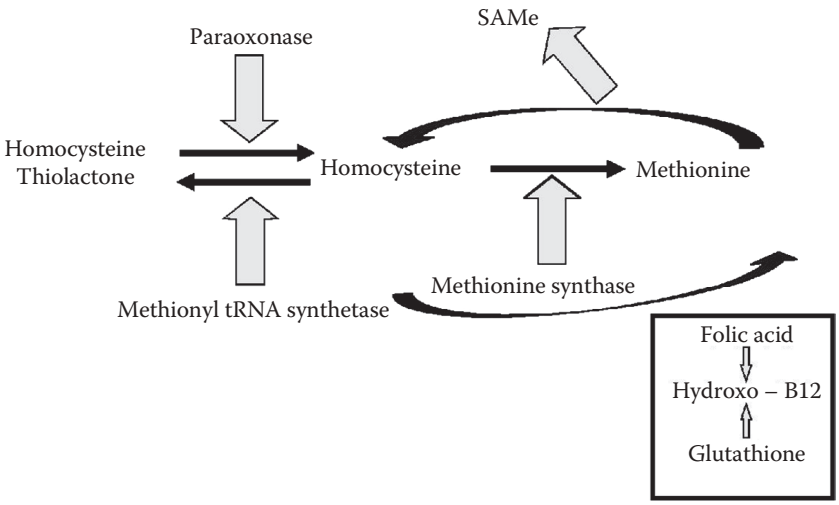

FIGURE 32.5 Thiolactone: Homocysteine thiolactone denatures proteins and promotes autoimmunity [46]. The tendency for this continuous destructive process is inevitable if methylation nutrients are unavailable. Paraoxonase draws thiolactone back into the loop. This enzyme is upregulated by methionine. Thus, this loop functions like a vortex. Paraoxonase is inhibited by mercury [47] and isoleucine [48]. Paraoxonase is carried by HDL protein. Thus, the association is drawn to hyperlipemias and insulin resistance, as comoribidities in elderly BPI.

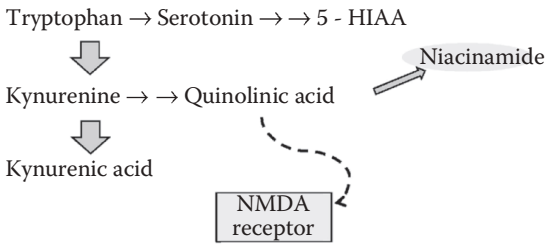

FIGURE 32.6 Quinolinic acid metabolism is critical to understanding inflammation in BPI and other neurologic conditions. Tryptophan shifts to the alternate kynurenine pathway, which provokes inflammation through quinolinic acid. Many neuropsychiatric conditions are dominated by this pathway. Excess quinolinic acid may be generated from the body as a whole—especially the liver.

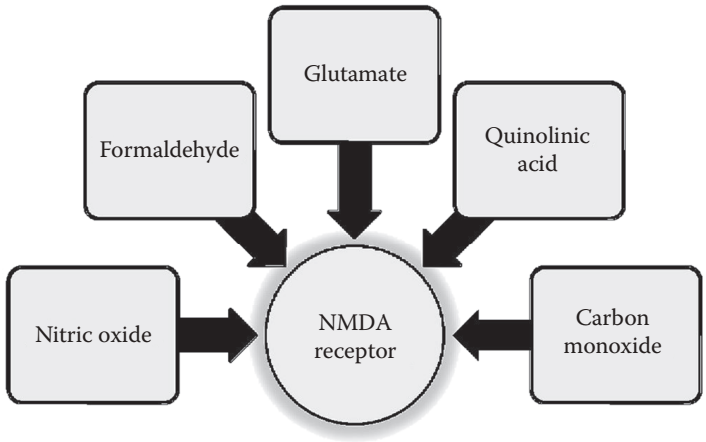

FIGURE 32.7. NMDA stimulation: multiple agonists trigger inflammation at the NMDA receptor site. These include formaldehyde, nitric oxide, glutamate, quinolinic acid, carbon monoxide, acid (H+ ion), and solvents.

blocks NF-Kappa B, along with curcumin, vitamin D3 [49], and the proteolytic enzyme bromelain. The higher order omega-3 fatty acids exert anti-inflammatory effects, which may underlie their demonstrated benefit in BPI [50].

PATIENT EVALUATION

Screening for Modifiable, External Environmental Factors

Modifiable, external, environmental factors exert direct, measurable, demonstrated effects on methylation. Identifying some of the factors is a critical step to patient treatment, especially the factors of which the patient is not aware and can be easily removed or reduced. These factors are categorized in Table 32.2 and examples from the authors' clinics include:

- Low level, chronic carbon monoxide poisoning.
- Home, school, and office construction including renovation materials, carpeting, and glues and paints that generate aldehydes. Once inhaled, these demand additional aldehyde scavenging from folate.
- Alcohol consumption leads to increased acetaldehyde as a metabolite and increases folate demand.
- Tobacco smoke contains many toxins that use up folate, hydroxocobalamin, glutathione, and vitamin C.
- The stress of travel, injury, altitude, and work stress can, alone or in combination, raise adrenalin production and its inactivation, both of which require additional SAMe for methylation. Dehydration can raise histamine levels, which further increases methylation demands for its inactivation [51].
- Orthopedic injuries require increased protein production through RNA synthesis for bone production and muscle rebuilding.
- Lyme and other tick-borne coinfections are associated with neuroinflammation.
- Housecats are underestimated as a source of occult viral infections, toxoplasmosis, and bartonellosis.
- Food poisoning and dysbiosis are associated with biotoxin production and decreased nutrient absorption.
- Indoor water damage and the resulting remediation and renovation are major sources of exposure. Particulates, microbes, indoor mold, and biotoxins secondary to water-damage stresses genetically predisposed persons. Resulting neuroinflammation, autoimmunity, and hormonal disruptions—including hypothyroidism and antidiuretic hormone depletion—are potential consequences.
- Microbicides can affect some people and can be found in construction materials as well as food residues.
- Renovation materials—new wallboard, synthetic carpet, padding, and paint—contain formaldehyde and other volatile hydrocarbons.
- Recent dental work and amalgam fillings contribute mercury and other toxic metals, which impair methylation (Figure 32.4).

Assessment of Concurrent Medical Conditions

Among the reasons BPI is associated with poor outcomes in concurrent medical conditions is common underlying metabolic dysfunction. Addressing the concurrent medical conditions can therefore correspondingly treat BPI. By way of illustration Table 32.3 lists the medical conditions concurrent in Vinitsky's patients with mood disorders.

TABLE 32.3
Concurrent Medical Diagnoses among Patients with Mood Disorders Presenting to Consultant Medical Practice

ICD	Diagnosis
270.8, 270.9	Amino Acid Deficiency
269.3	Mineral Deficiency (zinc, copper, selenium, magnesium, and others)
266.2	B12, B Vitamin Deficiency
080	Tick-borne: Lyme, Babesia, Ehrlichia, Bartonella
780	Fatigue
240–246	Thyroid Conditions
255	Adrenals (usually adrenal fatigue)
V83.89, V84	Genetic (polymorphisms)
780, 327.20	Sleep Apnea
337.1	Autonomic [includes all diagnoses or suspected]
279.9	Immune Disorder
401	Blood Pressure
985	Metals (mercury, cadmium, lead, arsenic, and others)
272	Cholesterol
281.0, 281.1	Pernicious Anemia & Other B12
470	Rhinitis
995.3	Environmental Sensitivities
337.1	Autonomic First Visit Only
493, 518.89, 786.09	Asthma, Restrictive, Short of Breath
082, 083,135	Rickettsia, Q Fever, Sarcoid
250	Diabetes
075, 078, 483	EBV, CMV, Mycoplasma
008.47, 112.85	Dysbiosis
346	Migraine
288	Neutropenia
729	Fibromyalgia
136	Parasite
691	Eczema
790.6	Low Iron (Ferritin)
414	Coronary Artery Disease
710, 711, 714	Rheumatoid, Lupus, Arthropathy
530	GERD
780.93	Memory Loss
696	Psoriasis
784	Headache
079, 058	Coxsackie Virus, Parvovirus, Herpes
344.9	Mitral Valve Prolapse
728	Muscle Spasm
277.6, 708, 995.1	Urticaria
021, 023, 130	Tularemia, Brucella, Toxoplasmosis
440	Atherosclerosis

These diagnoses were included in the differential diagnoses at the time of presentation and are presented in the order of relative frequency. Over eight years, 399 patients with psychiatric conditions carried 540 diagnoses. Those codes ranging from 290–320 are not included. Of those, 63 mood disorders (11.7%) were identified, the majority of which were major depressive disorders. ICD-9 codes are American Medical Association derived, and these designations correspond to *DSM IV–TR* codes of the American Psychiatric Association.

Assessment of the Internal Chemical Environment for Nutrients and Toxicants

In patients with BPI, evaluation of serum vitamin B12, folate, and homocysteine require additional explanation. When these tests are within the normal laboratory range and a patient has symptomatic BPI, a likely scenario is that vitamin B12 and folate are functionally low [52], and methionine is depleted so that the vitamin B12 and folate are underutilized. Once these patients' stress markers are treated with simultaneous hydroxocobalamin and folate, previously normal levels of these vitamins will rise until methionine deficiency is recognized by a homocysteine level less than 6, and must also be treated. In patients with mood disorders, B12 levels of less than 500 are frequently associated with ANS dysfunction providing additional evidence that levels are inadequate for the metabolic demands [53–55].

A high normal mean cell volume (MCV) is a marker for inefficient vitamin B12 utilization and often suggests glutathione inadequacy. Low MCV implies iron deficiency, which is also associated with fatigue, and low MCV can also represent lead toxicity or B6 deficiency. Since ineffective vitamin B12 utilization can be concurrent with iron deficiency, inadequate vitamin B6 or lead toxicity, an MCV at a normal level may merely represent averages of metabolic dysfunction.

Another laboratory test, less often utilized, is a 24-hour urine collection for amino acids. In Vinitsky's clinic, patients with mood disorders prior to methylation support are consistently low in four amino acids: phosphoethanolamine, hydroxyproline, asparagine, and isoleucine. As treatment progresses, these amino acids may begin to normalize, even without amino acid supplementation. Additional considerations are as follows:

- Choline can be synthesized from phosphoethanolamine (the first of four amino acid deficiencies described earlier) in a series of steps that eventually requires three SAMe molecules. If it remains functional as phosphatidyl choline, it can be incorporated into cell membranes. As a precursor to acetylcholine, choline [37] is often deficient. When choline is assimilated into acetylcholine, that process heals; but choline, when metabolized, generates its first metabolite as formaldehyde, which is potently hypersympathetic and requires folate to scavenge. Carnitine (tri-methyl lysine) and betaine (tri-methyl glycine) also require SAMe for proper synthesis, and should therefore be supplemented only after methylation support is initiated.
- Asparagine facilitates oligosaccharide synthesis in the pituitary, such as thyroid stimulating hormone (TSH) [56]. Asparagine depletion functions to protect adrenal function, which supercedes thyroid function. Patients with BPI are among the many patients who have low body temperature, but whose TSH is normal, and among those patients with altered salivary cortisol levels, but who are not diagnosed as adrenally insufficient by standard synthetic ACTH stimulation. However, by applying methylation treatments as a foundation, asparagine levels improve without supplementation, and TSH levels begin to rise, leading to detection of a previously hidden hypothyroid state.
- Isoleucine is a precursor to methylmalonic acid (MMA) [57], which yields succinic acid. This second step requires vitamin B12. MMA is often used as a marker for vitamin B12 deficiency, since this pathway is the only one exclusive to vitamin B12. This form of B12 is actually adenosylcobalamin, which forms from adenosine + activated OH-B12 (which depends on glutathione). It is hypothesized that as MMA increases due to vitamin B12 deficiency, isoleucine is not needed, resulting in its depletion. Over time, MMA will return to normal. Note that isoleucine or glutathione deficiency can result in normal MMA, even when vitamin B12 is also deficient. Thus, MMA is not a reliable predictor of B12 deficiency in chronic illness. Isoleucine also inhibits paraoxonase (see Figure 32.5). It is possible that the loss of isoleucine will allow paraoxonase to remain more active, permitting thiolactone to return to the pathway that generates SAMe and serving as an adaptive mechanism. Isoleucine reduces hepatic gluconeogenesis and drives glucose into muscle when fed to fasting rats [58]. Hence, isoleucine depletion may over time contribute to rising glucose and lead to insulin resistance and type 2 diabetes comorbidity of BPI.

Using Physical Evaluation of the Autonomic Nervous System as an Approach to Monitor Improvement in BPI

Typically, BPI criteria for improvement are reflected in stability of mood, functioning in different settings, and in clinical trials, a variety of administered screening scales. However, these parameters are focused on the disorder itself, not the broader ranging effects of methylation and other metabolic consequences. Stress manifests metabolically as increased malondialdehyde (oxidative stress), nitric oxide (inflammation stress), and the depletion of reduced glutathione. Glutathione may be measured, but at present, malondialdehyde and nitric oxide are not routinely measured, as these levels are in constant flux. However, the consequences of stress markers and their reduction can be observed through the autonomic nervous system [59–61].

Autonomic nervous system (ANS) dysfunction can be assessed in the review of symptoms, which include dizziness, especially on change of position, often presenting with cold hands and feet. When impaired, the ANS demonstrated a rigidity of function with the parasympathetic (PSNS) and sympathetic (SNS) systems not commensurate with physiologic demands (Table 32.4). Additional symptoms are balance disturbance in the dark (confirmed on physical exam with eyes closed), dry mucus membranes, lack or excess of secretions and sweating, unexplained shortness of breath and

TABLE 32.4
Neuropsychiatric and Behavioral Paradoxes May Manifest When the Autonomic Nervous System (ANS) Functions in a Rigid, Paradoxical Manner

Function	Sympathetic Overshoots or Parasympathetic Undershoots	Parasympathetic Overshoots or Sympathetic Undershoots
Sleep	Can't fall asleep, mid-sleep wakeups, early wakeups, phase shifts	Excessive sleepiness, daytime sleepiness
Behavior	Angry, impulsive, hyperactive, violent	Withdrawn, sluggish, lacking motivation
Concentration	Impaired	Impaired
Memory	Impaired	Impaired
Mood	Anxiety	Depression
Thinking	Altered	Altered
	Obsessive	Slowed
	Suicidal	Suicidal
Judgment	Impaired	Impaired
Movement	Tics, tremors, twitches, myoclonic jerks, hyperactivity	Not impaired
Electrical	Seizures	Not impaired
Coordination	Impaired	Impaired
Apraxia	Writing, speech–articulation	Not present
Balance	Dizziness	Impaired
Toe Balance	Impaired	Impaired
Heel-Toe Gait	Impaired	Impaired
Vertigo	Present	Not present
Socialization	Possible autistic spectrum	No consistent impairment

An "overshoot" represents the intrusion of an ANS branch into an organ system where it was not expected to be functioning. An "undershoot" means that one branch of the ANS does not perform as expected, thereby allowing its opposite to overperform. The more rigid the ANS, the wider are the swings and fluctuations. In the physical exam, balance disturbance with eyes closed reflects these gyrations. Contrast smooth efficient performance with overshoots/undershoots (overcompensation/undercompensation) of slow performance, missteps, truncal wobble, breathing disturbance—rapid breathing or breath-holding, sweating, eyes tearing, and nervous laughter.

palpitations, increased urinary frequency and nocturia, and altered gastrointestinal patterns. As more systems are affected, the greater the ANS impairment. Organs other than the adrenal glands are under PSNS control.

ANS dysfunction and improvements in function can be observed on physical exam as follows:

- Alterations in blood pressure and heart rate can be assessed at rest and with short-term position change, and, when necessary, standing in one position with no movement for up to five minutes. Changes may occur from supine to standing, with an excessively brisk rise in heart rate (30 beats per minute from supine to stand) such as seen in postural orthostatic tachycardia syndrome (POTS). Twenty-beat increases usually reflect dehydration, while drops in blood pressure without compensating rise in heart rate may indicate neuropathy or adrenal dysfunction. In Vinitsky's experience, white coat hypertension is autonomic dysfunction, with hidden or obvious mercury burden.
- Cold hands and feet are sometimes present, and the patient may report this as a chronic symptom.
- Jaw clicking implies temporo-mandibular joint dysfunction. It may also suggest an underlying impairment in ANS. The jaw is generally under PSNS control, as demonstrated by a yawn followed by a breath.
- Balance and coordination dysfunction can be present. The Romberg test is usually negative. Finger-nose and finger-finger testing are sometimes abnormal. Fine tremor may be present with increased sympathetic nervous system activity and mercury burden. Single-foot balance, toe balance, tandem heel-toe, and static heel-toe are used to establish baseline ANS testing and monitor progress with treatment. Balance tests can be conducted first with the patient's eyes open and then with them closed. Standardizing these balance tests for 10-second trials helps the comparison. Toe-balance trials (heels raised off the floor) are repeated five times with eyes closed, for up to 10 seconds each, after one or more baseline eyes-open trial of 10 seconds. Repeat sets gather more information. Interpretations: Inability to balance with eyes open implies sensory neuropathy. Impaired toe balance with eyes closed reflects stressful breathing (increased SNS when PSNS should be dominant). Improvements identify a learning curve, while decline in performance on repeat sets reflects fatigue. A second successful eyes-open trial performed for 10 seconds confirms the impairment during eyes closed. A second set of five, eyes closed, and third eyes open is confirmatory. For tandem heel-toe, 10 steps can be timed, forward and reverse. Errors are recorded. Normal in Vinitsky's clinic is 7–10 seconds without errors, eyes open or closed. Slower performance and more errors reflect greater ANS dysfunction. Static heel-toe substitutes for failure to complete tandem testing (when there is no physical disability), and suggests greater ANS impairment. Place right foot in front of left, eyes open for 10 seconds, then close eyes for up to 10 seconds additional. Repeat the trial with feet reversed. Also record body language such as rapid breathing, breath holding, truncal wobble, nervous laughter, paradoxical tears, frustration, anger, and so on.

TREATMENT CONSIDERATIONS

Drug Nutrient Interactions

Antidepressants

Antidepressants, such as citalopram or sertraline (selective serotonin reuptake inhibitors—SSRIs) raise serotonin levels by allowing serotonin to remain in the nerve synapses for a long period of time. Some patients may become paradoxically anxious if there are insufficient methylation resources available (see earlier discussion concerning methylation and quinolinic acid production).

A single-valent cation, lithium is a cousin of sodium and potassium in the Periodic Table of Elements. Lithium has been extensively studied and has been available by prescription since 1970,

as lithium carbonate to treat BPI. Even though lithium is a prescription medication, lithium orotate and lithium aspartate are available without a prescription in the United States and are regulated in the category of dietary supplements. These forms of lithium are bioactive and are sometimes found in supplements claiming to boost mood.

The daily lithium dietary intake as estimated by the Environmental Protection Agency (EPA) in 1985 was 650–3100 μg for a 70-kg man. Per Schrauzer, 1000 μg (1 mg) is a daily recommended amount [62]. Dietary sources of lithium are grains and green vegetables. There are no reports of lithium deficiency, but it is reasonable to speculate that such is possible, given lithium's favorable neurological benefits, relative to reversal of dementia, mood stabilization, rise in neurotransmitter levels, neuronal signaling, and neuronal protection [63,64].

Extensive research is available on lithium's mechanism of action [63–68]. Substantial data suggests that lithium favorably influences methylation to modify glutamate metabolism or its effects on dopamine. Lithium has a modifying influence on glutamate by downregulating the NMDA receptor.

However, lithium appears to have opposite effects on methylation—both upregulating and downregulating, depending on site of action. By supporting methylation lithium is more biochemically available to exert its neuropsychiatric benefit. Lyoo et al. reported no change in psychiatric scales while treating with oral choline supplementation, yet there was reduction in purine residues of BPI patients treated with lithium [69]. This observation is important because there appears to be a reworking of signaling pathways and gene expression over time with lithium [64].

Divalproex, or valproate, is thought to decrease DNA methylation of histones—an epigenetic phenomenon—thereby turning off the manic phase of BPI [27]. Another potential site of action is demethylation of GAD67 and GAD1 (glutamic acid decarboxylase) GABAergic promoter site. GAD converts glutamate to GABA, and like all decarboxylases is vitamin B6 dependent. In this scenario, glutamate levels will increase and will act as a brake on dopamine-induced psychosis and mania. Valproate has an effect on chromatin remodeling over time [70]. By contrast, lamotrigine acts on the NMDA receptor to lower glutamate levels, thereby improving depressed mood [71].

Anxiolytics

Anxiolytics such as clonazepam and lorazepam are benzodiazepines, which function by increasing GABA affinity at the $GABA_a$ receptor [72]. These may help, when there is already sufficient GABA being generated from glutamate via GAD65 or GAD67. Lorazepam will not work for mania. Clonazepam does have a reasonable effect on hypomania and mania but may still aggravate or trigger mania [73].

Antipsychotic Medications

Antipsychotic medications' actions are several. Aripiprazole is a complex-functioning dopamine partial agonist/antagonist plus a partial serotonin antagonist for serotonin $5HT_{2A}$ and an agonist for $5HT_{1A}$. If dopamine levels are low, then aripiprazole is a dopamine partial agonist, but when levels are high, then it functions as an antagonist. Risperidone mechanisms are similar to aripiprazole, except that there is no partial agonism for $5HT_1a$. Response rates when compared to placebo are modest in these medications, and their side effects unfavorably influence appetite, inflammation, and blood sugar [74–76] among other metabolic processes shown to burden the body's methylation pathways.

Support of Methylation as Adjunct Treatment

An initial approach to nutritional support of methylation is presented in Table 32.5. Start with 5 mg of folic acid (folate) and 2 mg of hydroxocobalamin (OH-B12) administered sublingually or transbuccally and repeat as needed. Many patients begin treatment on their own. However, for initial dosing, monitor anxious or hesitant patients in the office, while instructing self-monitoring of blood pressure and pulse. Notably, patients with a vitamin B12 level of less than 500 are more likely to have an "adrenalin rush" reaction (BP and pulse increase, feeling cold, jittery, head rush, hungry)

TABLE 32.5
An Approach Using Supplemental Nutrients

Basic 6 Nutrients	Strength	Formulation	Means of Administration	Usual Starting Doses
1. Folic Acid*	5 mg	Liquid, capsules, and tablets	Sublingual or oral	1–2 doses, 3 times daily
Initiate folic acid dosing in a 5 to 2 ratio with hydroxocobalamin—take a fixed ratio of 5 parts folate:2 parts hydroxocobalamin. Target doses: Note that the dosing here may exceed that of recommended use for dietary supplements and should therefore be implemented under physician guidance with monitoring as described.				
2. Hydroxocobalamin*	2 mg	Tablets	Sublingual or transbuccal	1–2 doses, 3 times daily
3. Vitamin C	1000 mg	Powder, tablets, (use buffered, ascorbic acid)	Oral (iv also available)	1–3 times daily
Target doses: Note that the dosing here exceeds that of recommended use for dietary supplements and should therefore be implemented under physician guidance.				
4. Magnesium	100 mg	Glycinate, malate, aspartate	Oral	2–3 times daily
Target doses: 200 mg, 2–3 times daily. Magnesium malate helps muscles relax and is sometimes used to aid sleep, while aspartate is energizing and should be avoided in patients with anxiety.				
5. Taurine	500 mg	Capsules	Oral	2–3 times daily
Target doses: 2 caps, 2–3 times daily. Note that taurine promotes homocysteine recycling and glutathione production.				
6. Vitamin B6	50 mg	Pyridoxine, Pyridoxal 5-phosphate	Oral	1–2 twice daily
Target doses: 1–2 caps, 2 times daily. This can be achieved using a multivitamin or vitamin B complex supplement. Note that vitamin B6 promotes vitamin B3 and histamine production [51].				

* **Folic acid and hydroxocobalamin should be taken simultaneously sublingually or transbuccally. The optimal ratio is 5:2. The number of doses daily depends on the extent of stress buildup, as reflected in stress markers.**

on their first one or two doses, and again, if they take doses too infrequently. It is thought that adrenals concentrate the first dose to make adrenalin, whereas subsequent doses distribute to tissues to inactivate adrenalin.

Multiple doses of folate/OH-B12 can be administered simultaneously, and patients should be encouraged to become flexible with doses, so long as they monitor and track their progress.

By contrast, intravenous hydroxocobalamin as a sole agent has been introduced to treat cyanide poisoning in 5 gm (5000 mg) doses with successful outcomes. In a study of 136 normal volunteers who received up to 10 gm hydroxocobalamin IV over 30 min, transient rise in blood pressure was observed in some healthy volunteers. Other side effects included "pustular/papular rash, headache, erythema at the injection site, decrease in lymphocyte percentage, nausea, pruritus, chest discomfort, and dysphagia". Two instances of allergy were observed [77].

Supporting nutrients are vitamin C (ascorbate), magnesium, taurine, and vitamin B6, which encourage production and sustained activity of reduced glutathione. Folate and hydroxocobalamin require reduced glutathione. Glutathione and vitamin C are paired antioxidants. The more powerful antioxidant molecule donates its electrons to the oxidized one. Therefore, presence of oxidized ascorbate will result in a shortage of reduced glutathione, since the latter will work to reduce ascorbate.

Glutathione (GSH) supplementation is required when supporting nutrients with additional N-acetyl cysteine (NAC) cannot improve the speed of dissolution of folate/OH-B12 combination in a nonresponding patient. A clue is a rising MCV in the face of current folate/OH-B12dosing. An explanation may include rapid degradation of GSH by gamma-glutamyl transaminase (GGT), releasing excess glutamate. Topical dosing is useful because the skin appears to function as a gate for the body's needs, just as the mucus membranes perform with folate/OH-B12. Sometimes even a small dose of GSH may suddenly speed up folate/OH-B12 dissolution, resulting in the aforementioned adrenalin rush.

Response can be monitored through laboratory testing and other parameters in several ways:

- During treatment at home, patients should keep a diary, recording BP and P, while tracking symptoms and other parameters. These may include the timing of sleep, diet, medications, supplements, relative to the doses of basic 6 nutrients. If BP becomes too low, adjustments of BP medications or hydration may be required. Normalization of methylation should be regarded as primary, as medication doses can often be reduced.
- Homocysteine should be monitored every three months. When it drops below 6 that implies methionine deficiency, which requires methionine supplementation to raise homocysteine back to 6. Such addition increases the power to make more SAMe as the patient needs it, which results in further repair and healing.
- MCV should be monitored every three months. MCV should move toward the middle of the reported lab normal range. Failure to do so reflects impaired B12 utilization, and adjustments in treatment are required.
- Urinary amino acids should begin to normalize phosphoethanolamine, asparagine, and isoleucine. Additional deficiencies may also correct. Timing of improvement may take three to six months, when testing is repeated. Further improvements of these require amino supplementation.
- Immune function improves and autoimmunity decreases, as methylation capacity improves.
- Parameters reflecting other medical conditions that were previously identified and environmental exposures that have been reduced, should improve. These may include metals, inflammation markers relative to mold biotoxins, and antibodies or other indicators relative to infections.
- Response to medications improves and over time need for medication doses reduces.
- Suspect or incorporate into testing any newly uncovered environmental exposure during review of a relapsed or nonresponsive patient.
- To date, genetic testing has not been repeated but may be appropriate over time to document if various polymorphisms have righted themselves through methylation treatment.

Metabolic Approaches to Poor Initial Treatment Response

Most often, responders begin to improve in days to weeks. Suspect nonresponders when treatments work intermittently or improvement simply stops. Also, suspect nonresponders when patient feels no change of daytime alertness, or sense of calm when doses are administered, or ease in preparing to sleep with absence of light. Another sign is the failure of BP and P to decrease after doses or to trend downward overtime.

In Vinitsky's approach, it is important to effectively clean up stress markers with folate/OH-B12 scavenger nutrients, after which methylation can proceed more effectively. Therefore, fixed daily doses is not the rule but a starting point in treatment. Quickly dissolving folate/OH-B12 in the presence of symptoms informs the patient to raise the doses at least in the short term.

Another common cause of poor response is that folate and hydroxocobalamin are dissolving slowly. Always inquire if hydroxocobalamin is used, since patients may substitute methylcobalamin

or cyanocobalamin, thinking that these are equivalent. Infrequent dosing will result in a wear-off effect (i.e., return of symptoms), when there are abundant stress markers.

The primary underlying metabolism of nonresponse is that glutathione (GSH) is inactive, not present, not being created, or excessively metabolized. Nutrients to support glutathione can be beneficial.

Additional actions include the need to adjust medications, or re-evaluate recent adjustments. This may account for difficulties, when nutrients are added to an ongoing treatment regimen. At times, the previously dosed medication has become too powerful and should be titrated downward. Medication dosing can lead to thyroid and/or adrenal imbalances. Patients taking benzodiazepines for anxiety are more likely to be slow or nonresponders, based on the authors' clinical observations.

Occasionally, MTHFR–C677T, A1298C homozygous for either one, or heterozygous for both, will compromise folate activation. If homocysteine has always been close to normal, then this is not likely a viable issue, but active folate (methyltetrahydrofolate—800 mcg daily) can be added, while continuing folate and hydroxocobalamin at the same doses.

It may be appropriate to test for a COMT (C-O-Methyltransferase) SNP. Someone homozygous for a COMT polymorphism will have slowed utilization of SAMe for catechol metabolism. Mercury can compound this genetic susceptibility.

Hemopyrroluria, if present, has been shown to lead to loss of vitamin B6, zinc, and other nutrients [78] involved in methylation.

Underlying environmental factors and inflammation may be ongoing.

CLINICAL SUMMARY

Bipolar illness in its many forms is a serious, stubborn psychiatric condition. Methylation and other supportive treatments have the potential to positively influence the reduction in symptoms. Given the magnitude that hypomethylation plays in the expression of bipolar symptoms, methylation treatments should be strongly considered for their benefits in improving outcomes. Methylation is also relevant to physician awareness of drug-nutrient interactions in the treatment of BPI and is one possible underlying factor in medication tachyphylaxis. The authors' approach to methylation and correcting metabolic dysfunction are presented.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Text Revision, DSM-IV-TR.* Fourth edition. Washington, DC: American Psychiatric Association, 2000.
2. Merikangas, KR, R Jin, JP He, et al. "Prevalence and correlates of bipolar spectrum disorder in the World Mental Health Survey Initiative." *Arch Gen Psychiatry* 68, no. 3 (2011): 241–51.
3. Wolkenstein, L, K Bruchmuller, P Schmid, and TD Meyer. "Misdiagnosing bipolar disorder—Do clinicians show heuristic biases?" *Journal of Affective Disorders* 130, no. 3 (2011): 405–12.
4. Frye, MA. "Diagnostic dilemmas and clinical correlates of mixed states in bipolar disorder." *J Clin Psychiatry* 69, no. 5 (2008): e13.
5. Chen, P, I Korobkova, K Busby, and M Sajatovic. "Managing late life bipolar disorder: An update." *Aging Health* 7, no. 4 (2011): 557–71.
6. Calabrese, JR. "Overview of patient care issues and treatment in bipolar spectrum and bipolar II disorder." *J Clin Psychiatry* 69, no. 6 (2008): e18.
7. McIntyre, RS, JK Soczynska, JL Beye, et al. "Medical comorbidity in bipolar disorder: Re-prioritizing unmet needs." *Curr Opin Psychiatry* 20, no. 4 (2007): 406–16.
8. Frasure-Smith, N F Lesperance, and M Talajic. "Depression following myocardial infarction. Impact on 6-month survival." *JAMA*, 270 (Oct 1993): 1819–25.
9. Garcia-Portilla, MP, et al. "Cardiovascular risk in patients with bipolar disorder." *Jl of Affective Disorders* 115, no. 3 (Jun 2009): 302–8.
10. Judd, LL, et al. "Residual symptom recovery from major affective episodes in bipolar disorders and rapid episode relapse/recurrence." *Arch Gen Psychiatry* 65, no. 4 (2008): 386–94.

11. Kessler, RC, P Berglund, O Demler, R Jin, KR Merikangas, and EE Walters. "Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication." *Arch Gen Psychiatry* 62 (2005): 593–602.
12. Laursen, TM, T Munk-Olsen, E Agerbo, C Gasse, and PB Mortensen. "Somatic hospital contacts, invasive cardiac procedures, and mortality from heart disease in patients with severe mental disorder." *Arch Gen Psychiatry* 66 (July 2009): 713–20.
13. Crow, S. "Bipolar disorder: Part 1, recent advances in the treatment of bipolar disorder." *Audio Digest Psychiatry.* 39, no. 4 (Feb 21, 2010).
14. Judd, LL, HS Akiskal, PJ Schettler, et al. "A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder." *Arch Gen Psychiatry* 60–9 (2003): 261.
15. Judd, LL, HS Akiskal, PJ Schettler, et al. "The long-term natural history of the weekly symptomatic status of bipolar I disorder." *Arch Gen Psychiatry* 59 (2002): 530–37.
16. van der Schot, AC, R Vonk, RGH Brans, et al. "Influence of genes and environment on brain volumes in twin pairs concordant and discordant for bipolar disorder." *Arch Gen Psychiatry* 66, no. 2 (2009): 142–51.
17. Baum, AE, N Akula, M Cabanero, et al. "A genome-wide association study implicates diacylglycerol kinase eta (DGKH) and several other genes in the etiology of bipolar disorder." *Molecular Psychiatry* 13, no. 2 (Feb 2008): 197–207.
18. Wellcome Trust Case Control Consortium. "Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls." *Nature* 447, no. 7145 (Jun 2007): 661–78.
19. Sklar P, Smoller JW, Fan J, et al. "Whole-genome association study of bipolar disorder." *Molecular Psychiatry* 13, no. 6 (Jun 2008): 558–69.
20. Ferreira MA, O'Donovan MC, et al. "Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder." *Nature Genetics* 40, no. 9 (Sep 2008): 1056–58.
21. Sklar P, Ripke S, Scott LJ, et al. "Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4." *Nature Genetics* 43, no. 10 (Sep 2011): 977–83.
22. Roybal K, Theobold D, Graham A, et al. "Mania-like behavior induced by disruption of CLOCK." *Proceedings of the National Academy of Sciences of the United States of America* 104, no. 15 (Apr 2007): 6406–11.
23. Bhagwagar, Z. "New findings in childhood bipolar disorder—Diagnostic issues in pediatric bipolar disorder." *Medscape.* July 15, 2008. http://www.medscape.org/viewarticle/577360.
24. Frans EM, S Sandin, A Reichenberg, et al. "Advancing paternal age and bipolar disorder." *Arch Gen Psychiatry* 65, no. 9 (Sep 2008): 1034–40.
25. Jirtle, R, A Bernal, and D Skaar. *Epigenetic Medicine*. Edited by Robert A. Meyers. Wiley-VCH Verlag Gmb H & Co. KGaA. October 2011. http://onlinelibrary.wiley.com/doi/10.1002/3527600906.mcb.201100010/pdf (accessed December 26, 2011).
26. Feng, J, S Fouse, and G Fan. "Epigenetic regulation of neural gene expression and neuronal function." *Pediatric Research* 61, no. 5, Pt 2 (2007): 58R–63R.
27. McGowan, PO, and T Kato. "Epigenetics in mood disorders." *Environ Health Prev Med* 13 (2008): 16–24.
28. Higuchi, F, S Uchida, Yamagata H, et al. "State-dependent changes in the expression of DNA of methyltransferases in mood disorder patients." *Journal of Psychiatric Research* 45 (2011): 1295–1300.
29. Rodenhiser, D, and M Mann. "Epigenetics and human disease: Translating basic biology into clinical applications." *CMAJ* 174, no. 3 (2006): 341–48.
30. Ghadirivasfi, M, S Nohesara, H-R Ahmadkhaniha, et al. "Hypomethylation of the serotonin receptortype-2A gene (HTR2A) at T102C polymorphic site in DNA derived from the saliva of patients with schizophrenia and bipolar disorder." *American Journal of Medical Genetics Part B Neuropsychiatric Genetics* 156, no. 5 (2011): 536–45.
31. Nohesara, S, M Ghadirivasfi, S Mostafavi, et al. "DNA hypomethylation of MB-COMT promoter in the DNA derived from saliva in schizophrenia and bipolar disorder." *Journal of Psychiatric Research* 45, no. 11 (2011): 1432–38.
32. Chen, Y, E Dong, and DR Grayson. "Analysis of the GAD1 promoter: Trans-acting factors and DNA methylation converge on the 5′ untranslated region." *Neuropharmacology* 60 (2011): 1075–87.
33. Mehler, MF, and JS Mattick. "Non-coding RNAs in the nervous system." *J Physiol* 575, no. 2 (2006): 333–41.
34. Konradi C, M Eaton, M MacDonald, et al. 2004. "Molecular evidence for mitochondrial dysfunction in bipolar disorder." Source Archives of *Arch Gen Psychiatry* 61, no. 3 (2004): 300–308. [Erratum appears in *Arch Gen Psychiatry* 61, no. 6 (2004): 538.]
35. Shin, K, A Schaffer, AJ Levitt, and MH Boyle. "Seasonality in a community sample of bipolar, unipolar and control subjects." *Jl of Affective Disorders* 86, no. 1 (2005): 19–25.

36. Rappoport, SM and MT Smith. "Epidemiology: Environment and disease risks." *Science* 330, no. 6003 (Oct 2010): 460–61.
37. Debray, F-G, Y Boulanger, A Khiat, et al. "Reduced brain choline in homocystinuria." *Neurology* 71 (2008): 44–49.
38. Walsh, W. Dr. William Walsh on histamine levels at outreach 2010. 2010. http://www.biobalance.org.au/videos/post/21 (accessed January 30, 2012).
39. Onyango, AN, and N Baba. "New hypotheses on the formation of malondialdehyde and isofurans." *Free Radic Biol Med* 49, no. 10 (2010): 1594–1600.
40. Pall, ML, and JH Anderson. "The vanilloid receptor as a putative target of diverse chemicals in multiple chemical sensitivity." *Archives of Environmental Health* 59, no. 7 (2004): 363–75.
41. Rao, JS, JG Harry, SI Rapoport, and H-W Kim. "Increased excitoxicity and neuroinflammatory markers in postmortem frontal cortex from bipolar disorder patients." *Mol Psychiatry* 15, no. 4 (April 2010): 384–92.
42. Duguid, IC and TG Smart. Chapter 14, Presynaptic NMDA Receptors, in *Biology of the NMDA Receptor*, AM Van Dongen, ed. Boca Raton, FL: CRC Press, 2009.
43. Oppeneer, SJ, YA Ross, WP Koh, et al. "Genetic variationi in folylpolyglutamate synthase and gamma-glutamyl hydrolase and plasma homocysteine levels in the Singapore Chinese health study." *Molecular Genetics & Metabolism* 105, no. 1 (2012): 73–78.
44. Jang, S, HS Jeong, JS Park, et al. "Neuroprotective effects of (-)-epigallocatechin-3-gallate against quinolinic acid-induced excitotoxicity via PI3K pathway and NO inhibition." *Brain Research* 1313 (Feb 2010): 25–33.
45. Braidy, N, R Grant, S Adams, and GJ Guillemi. "Neuroprotective effects of naturally occurring polyphenols on quinolinic acid-induced excitoxocity in human neurons." *FEBS Journal*, (2010): 368–82.
46. Jakubowski, H. "Homocysteine-thiolactone: metabolic origin and protein homocysteinylation in humans." *J Nutr* 130 (2000): 377S–381S.
47. Houston, MC. "Role of Mercury Toxicity in Hypertension, Cardiovascular Disease, and Stroke." *Journal of Clinical Hypertension* 13 (2011): 621–27.
48. Jakubowski, H. "Calcium-dependent human serum homocysteine thiolactone hydrolase." *Jl Biological Chemistry* 275, no. 6 (2000): 3957–62.
49. Hoang, MTT, LF DeFina, BL Willis, et al. "Association between low 25-hydroxyvitamin D and depression in a large sample of healthy adults: The Cooper Center longitudinal study." *Mayo Clin Proc* 86, no. 11 (2011): 1050–55.
50. Adibhatia, RM, and JF Hatcher. "Altered lipid metabolism in brain injury and disorders." *Subcell Biochem* 49 (2008): 241–68.
51. Haas, HL, OA Sergeeva, and O Selbach. "Histamine in the nervous system." *Physiol Rev* 88 (2008): 1183–1241.
52. Lambie, DG, and RH Johnson. "Drugs and folate metabolism." *Drugs* 30, no. 2 (Aug 1985): 145–55.
53. Beitzke, M, P Pfister, J Fortin, and F Skrabal. "Autonomic dysfunction and hemodynamics in B12 deficiency." *Autonomic Neuroscience: Basic and Clinical* 97 (2002): 45–54.
54. Fine, EJ, and ED Soria. "Myths about vitamin B12 deficiency." *Southern Medical Journal* 84, no. 12 (1991): 1475–81.
55. Eisenhofer, G, DG Lambie, RH Johnson, EA Tan, and E Whiteside. "Deficient catecholamine release as the basis of orthostatic hypotension in pernicious anemia." *Journal of Neurology, Neurosurgery & Psychiatry* 45, no. 11 (1982): 1053–55.
56. Fares, FA, N Gruener, and Z Kraiem. "The role of the asparagine-linked oligosaccharides of the alpha-subunit in human thyrotropin bioactivity." *Endocrinology* 137, no. 2 (1996): 555–60.
57. Moelby L, K Rasmussen, MK Jensen, et al. "Serum methyl malonic acid before and after oral L-isoleucine loading in cobalamin-deficient patients. *Scand J Clin Lab Invest* 52, no. 4 (Jun 1992): 255–59.
58. Doi, M, I Yamaoka, M Nakayama, et al. "Hypoglycemic effect of isoleucine involves increased muscle glucose uptake and whole body glucose oxidation and decreased hepatic gluconeogenesis." *American Journal of Physiology, Endocrinology, and Metabolism* 292, no. 6 (Jun 2007): E1683–93.
59. Cetiner, M, G Sener, AO Sehirli, et al. "Taurine protects against methotrexate-induced toxicity and inhibits leukocyte death." *Toxicology & Applied Pharmacology* 209, no. 1 (Nov 2005): 39–50.
60. Surwit, RS, MS Schneider, and MN Feinglos. "Stress and Diabetes." *Diabetes Care* 15, no. 10 (Oct 1992): 1413–22.
61. Watson, WP, T Munter, and BT Golding. "A new role for glutathione: Protection of vitamin B12 from xenobiotics." *Chem Res Toxicol* 17, no. 12 (2004): 1562–67.
62. Schauzer, GN. "Lithium: Occurrence, dietary intakes, nutritional essentiality." *Journal of the American College of Nutrition* 21, no. 1 (Feb 2002): 14–21.

63. Jope, RS. "Anti-bipolar therapy: Mechanism of action of lithium." *Molecular Psychiatry* 4 (1999): 117–28.
64. Chiu, C and D Chuang. "Molecular actions and therapeutic potential of lithium in preclinical and clinical studies of CNS disorders." *Pharmacologic Therapy* 128, no. 2 (2010): 281–304.
65. D'Addario, C, B Dell'Osso, M Palazzo, et al. "Selective DNA methylation of BDNF promoter in bipolar disorder: Differences among patients with BD I and BD II." *Neuropsychopharmacology* 37, no. 7 (Jun 2012): 1647–55.
66. Popkie, AP, LC Zeidner, AM Albrecht, et al. "Phosphatidyl inositol 3-kinase (PI3K) signaling via glycogen synthase kinase-3 (gsk-3) regulates DNA methylation of imprinted loci." *Journal of Biological Chemistry* 285, no. 53 (2010): 41337–47.
67. Chen, C-L, CF Lin, CW Chiang, et al. "Lithium inhibits ceramide- and etoposide-induced protein phosphatase 2A methylaion, Bcl-2 dephosphorylation, caspase-2 activation, and apoptosis." *Mol Pharmacol*, 70 (2006): 510–17.
68. Bremer, T, C Diamond, R McKinney, et al. "The pharmacogenetics of lithium response depends upon clinical co-morbidity." *Molecular Diagnosis & Therapy* 11, no. 3 (2007): 161–70.
69. Lyoo, IK, CM Demopulos, F Hirashima, et al. "Oral choline decreases brain purine levels in lithium-treated subjects in rapid-cycling bipolar disorder: A double-blind trial using proton and lithium magnetic resonance spectroscopy." *Bipolar Disorders* 5, no. 4 (2003): 300–306.
70. Dong, E, DR Grayson, A Guidotti, and E Costa. "Antipsychotic drug types can be characterized by their ability to modify GABAergic promoter methylation." *Epigenomics* 1, no. 1 (2009): 201–11.
71. Tsapakis, EM, and MJ Travis. "Glutamate and psychiatric disorders." *Advances in Psychiatric Treatment* 8 (2002): 189–97.
72. Brambilla, P, G Perez, F Barale, et al. "GABAergic dysfunction in mood disorders." *Molecular Psychiatry* 8 (2003): 731–37.
73. Curtin, F, and P Schulz. "Clonazepam and lorazepam in acute mania: A Baynesian meta-analysis." *Journal of Affective Disorders* 78, no. 3 (2004): 201–8.
74. Potkin, SG, AR Saha, MK Kujawa, et al. "Aripiprazole, a novel anti-psychotic, and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder." *Archives General Psychiatry* 60, no. 7 (2003): 681–90.
75. Fountoulakis, KN, and E Vieta. "Efficacy and safety of aripiprazole in the treatment of bipolar disorder: A systematic review." *Annals of General Psychiatry* 8, no. 16 (2009): 16–30.
76. Blanke, ML and AMJ VanDongen. Chapter 13, Activation Mechanisms of the NMDA Receptor, in *Biology of the NMDA Receptor*, AM Van Dongen, ed. Boca Raton, FL: CRC Press, 2009.
77. Uhl, W, Nolting, A. Golor, G, et al. "Safety of hydroxocobalamin in healthy volunteers in a randomized, placebo-controlled study." Clinical Toxicology: The Official Journal of the American Academy of Clinical Toxicology & European Association of Poisons Centres & Clinical Toxicologists, Suppl 44 (2006): 1:17–28.
78. Hoffer, A. "The discovery of kryptopyrrole and its importance in diagnosis of biochemical imbalances in schizophrenia and in criminal behavior." *J Orthomolecular Medicine* 10, no. 1 (1995): 3–7.
79. Bell IR, CM Baldwin, and GE Schwartz. "Sensitization studies in chemically intolerant individuals: Implications for individual difference research." *Annals of the New York Academy of Sciences* 933 (Mar 2001): 38–47.
80. Smulders YM, DEC Smith, RM Kok, et al. "Cellular folate vitamer distribution during and after correction of vitamin B12 deficiency: A case for the methylfolate trap." *British Journal of Haematology* 132, no. 5 (Mar 2006): 623–29.